Diabetes: foot ulcers and amputations

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ABSTRACT

INTRODUCTION: Diabetic foot ulceration is full-thickness penetration of the dermis of the foot in a person with diabetes. Severity is classified using the Wagner system, which grades it from 1 to 5. The annual incidence of ulcers among people with diabetes is 2.5% to 10.7% in resource-rich countries, and the annual incidence of amputation for any reason is 0.25% to 1.8%. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent foot ulcers and amputations in people with diabetes? What are the effects of treatments in people with diabetes with foot ulceration? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 50 systematic reviews and RCTs that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: debridement, human cultured dermis, human skin equivalent, patient education, pressure off-loading with felted foam or pressure-relief half-shoe, pressure off-loading with total-contact or non-removable casts, screening and referral to foot-care clinics, systemic hyperbaric oxygen for non-infected ulcers, systemic hyperbaric oxygen in infected ulcers, therapeutic footwear, topical growth factors, and wound dressings.

QUESTIONS

INTERVENTIONS

Key points

- Diabetic foot ulceration is full-thickness penetration of the dermis of the foot in a person with diabetes. Severity is classified using the Wagner system, which grades it from 1 to 5.

  The annual incidence of ulcers among people with diabetes is 2.5% to 10.7% in resource-rich countries, and the annual incidence of amputation for any reason is 0.25% to 1.8%.

  For people with healed diabetic foot ulcers, the 5-year cumulative rate of ulcer recurrence is 66% and of amputation is 12%.

- The most effective preventive measure for major amputation seems to be screening and referral to a foot-care clinic if high-risk features are present.

  Other interventions for reducing the risk of foot ulcers include wearing therapeutic footwear and increasing patient education for prevention, but we found no sufficient evidence to ascertain the effectiveness of these treatments.

- Pressure off-loading with total-contact casting or non-removable fibreglass casts successfully improves healing of ulcers.

  Removable-cast walkers rendered irremovable seem equally effective, but have the added benefit of requiring less technical expertise for fitting.

  We don't know whether pressure off-loading with felted foam or pressure-relief half-shoe is effective in treating diabetic foot ulcers.

- Human skin equivalent (applied weekly for a maximum of 5 weeks) seems better at promoting ulcer healing than saline-moistened gauze.

  Human cultured dermis does not seem effective at promoting healing.

- Topical growth factors seem to increase healing rates, but there has been little long-term follow-up of people treated with these factors.
- Systemic hyperbaric oxygen seems to be effective in treating people with severely infected ulcers, although it is unclear whether it is useful in people with non-infected, non-ischaemic ulcers.
- We don't know whether debridement or wound dressings are effective in healing ulcers.

  However, debridement with hydrogel and dimethyl sulfoxide wound dressings does seem to help ulcer healing.

  Debridement and wound dressings have been included together because the exact mechanism of the treatment can be unclear (e.g., hydrogel).

DEFINITION

Diabetic foot ulceration is full-thickness penetration of the dermis of the foot in a person with diabetes. Ulcer severity is often classified using the Wagner system. [1] **Grade 1** ulcers are superficial ulcers involving the full skin thickness but no underlying tissues. **Grade 2** ulcers are deeper, penetrating down to ligaments and muscle, but not involving bone or abscess formation. **Grade 3** ulcers are deep ulcers with cellulitis or abscess formation, often complicated with osteomyelitis. Ulcers with localised gangrene are classified as **Grade 4**, and those with extensive gangrene involving the entire foot are classified as **Grade 5**.

INCIDENCE/ PREVALENCE

Studies conducted in Australia, Finland, the UK, and the USA have reported the annual incidence of foot ulcers among people with diabetes as 2.5% to 10.7%, and the annual incidence of amputation for any reason as 0.25% to 1.8%. [2] [3] [4] [5] [6] [7] [8] [9] [10] [11]

AETIOLOGY/ RISK FACTORS

Long-term risk factors for foot ulcers and amputation include duration of diabetes, poor glycaemic control, microvascular complications (retinopathy, nephropathy, and neuropathy), peripheral vascular disease, foot deformities, and previous foot ulceration or amputation. [1] [2] [3] [4] [5] [6] [7] [8] [9] [11] Strong predictors of foot ulceration are altered foot sensation, foot deformities, and previous foot ulcer or amputation of the other foot (altered sensation: RR 2.2, 95% CI 1.5 to 3.1; foot deformity: RR 3.5, 95% CI 1.2 to 9.9; previous foot ulcer: RR 1.6, 95% CI 1.2 to 2.3; previous amputation: RR 2.8, 95% CI 1.8 to 4.3). [10]

PROGNOSIS

In people with diabetes, foot ulcers frequently co-exist with vascular insufficiency (although foot ulcers can occur in people with no vascular insufficiency) and may be complicated by infection. Amputation is indicated if disease is severe or does not improve with conservative treatment. As well as affecting quality of life, these complications of diabetes account for a large proportion of the healthcare costs of dealing with diabetes. For people with healed diabetic foot ulcers, the 5-year cumulative rate of ulcer recurrence is 66%, and of amputation is 12%. [12] Severe infected foot ulcers are associated with an increased risk of mortality.

AIMS OF INTERVENTION

To prevent diabetic foot complications, including ulcers and amputations; and to improve ulcer healing and prevent amputations where ulcers already exist, with minimum adverse effects.

OUTCOMES

Ulcer development rates: rates of development or recurrence of foot ulcers or major foot lesions; **amputation rates:** surgical removal of all or part of the lower extremity, major amputation or minor amputation; **ulcer healing rate:** time ulcers take to heal, or the proportion healed in a given period; rates of hospital admission; **infection rates:** rates of foot infection; **adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal September 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2010, Embase 1980 to September 2010, and The Cochrane Database of Systematic Reviews, September 2010 [online] (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and

odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 42). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions to prevent foot ulcers and amputations in people with diabetes?**

OPTION **SCREENING AND REFERRAL TO FOOT-CARE CLINICS**

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- The most effective preventive measure for major amputation seems to be screening and referral to a foot-care clinic if high-risk features are present.

Benefits and harms

Screening and referral to foot-care clinics versus usual care:

We found one systematic review (search date 1998, 1 RCT, 2001 people attending a general diabetes clinic). [13] The RCT included in the review compared a diabetes screening and protection programme (in high-risk people) with usual care (in people not screened for level of risk) over 2 years. [14]

Ulcer development

Screening and referral to foot-care clinics compared with usual care A diabetes screening and referral programme is no more effective at reducing the incidence of foot ulcers over 2 years in high-risk people (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer development					
[14] RCT	2002 people In review [13]	**Ulcer development , 2 years** 24/1001 (2%) with diabetes screening programme 35/1001 (4%) with usual care	P <0.14	⟷	Not significant

Amputation rates

Screening and referral programme compared with usual care A diabetes screening and referral programme is more effective at reducing the rate of major amputation over 2 years in people at high risk of foot ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Amputation rates					
[14] RCT	2002 people In review [13]	**Major amputation , 2 years** 1/1001 (0.1%) with diabetes screening programme 12/1001 (1.2%) with usual care	ARR 1.1% P <0.01 NNT 91 95% CI 53 to 250 P <0.04	●○○	diabetes screening programme

Infection rates

No data from the following reference on this outcome. [13]

Ulcer healing rate

No data from the following reference on this outcome. [13]

Adverse effects

No data from the following reference on this outcome. [13]

Further information on studies

[14] People in the diabetes screening and protection programme were screened for deficits in pedal pulses, light touch, and vibration sensation. People with persistent abnormal findings were referred to the diabetic foot clinic if they had a history of foot ulcer, were found to have a low ankle–brachial index (<0.75), or were noted to have foot deformities. The clinic provided podiatry and protective shoes as well as education regarding foot care. Usual care consisted of the normal follow-up for people in the clinic, who could be referred to the foot-care clinic by a healthcare professional.

Comment: **Clinical guide:**
Identifying individuals at high risk of foot complications is universally recognised as a key part of optimal care of people with diabetes mellitus. Being aware of locally available foot-care clinics is important to facilitate appropriate referrals of high-risk individuals.

OPTION EDUCATION

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- We don't know whether patient education is effective in preventing foot ulcers or amputations in people with diabetes.

Benefits and harms

Education versus usual care:

We found one systematic review [15] (search date 2001, 3 RCTs, [1 reported in 2 publications] [16] [17] [18] [19] , one quasi-randomised trial [20]), and one subsequent RCT. [21]

Ulcer development

Compared with usual care We don't know whether patient education is more effective at reducing the risk of developing foot ulcers (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer development					
[16] RCT	352 people with diabetes attending 4 primary-care teams, randomised by primary-care team In review [15]	**Serious foot lesions , 12 months** with structured care with usual care Absolute results not reported Structured care involved a patient education session about foot care	OR 0.41 95% CI 0.16 to 1.00	●●○	structured care

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		plus patient follow-up reminders plus prompts to healthcare providers to examine feet and provide education Usual care was not described			
[16] RCT	352 people with diabetes attending 4 primary-care teams, randomised by primary-care team In review [15]	**All foot lesions , 12 months** with structured care with usual care Absolute results not reported Structured care involved a patient education session about foot care plus patient follow-up reminders plus prompts to healthcare providers to examine feet and provide education Usual care was not described	OR 0.65 95% CI 0.36 to 1.17	⟷	Not significant
[18] [19] RCT	530 people with diabetes without any obvious need for foot care In review [15]	**Ulcer rates , after 7 years** 0.6% with education plus podiatric visits 0.6% with written foot-care instructions Absolute numbers not reported Education was delivered by a podiatrist and involved a 45-minute session covering footwear, hygiene, toenail cutting, emollient cream, avoiding risk, foot gymnastics, and preventive podiatric care plus podiatric visits of 30 to 60 minutes' duration for 1 year (as many times as judged appropriate by the podiatrist)	P = 1.0	⟷	Not significant
[20]	227 people with diabetes, allocated according to social security number In review [15]	**Ulcer recurrence , after 2 years** 5% with foot-care education 15% with routine diabetes education Absolute numbers not reported Foot-care education involved a single 1-hour educational class about foot care	RR 0.31 95% CI 0.15 to 0.65 NNT 10 95% CI 6 to 26	●●○	foot-care education
[21] RCT	178 people with diabetes mellitus with a healed foot ulcer	**Ulcer development , 6 months** 26/87 (30%) with foot-care education 18/85 (21%) with usual care Foot-care education involved a leaflet and a single individual 1-hour education session along with follow-up telephone call 1 month later Usual care involved the same foot-care leaflet but otherwise managed according to usual practice	RR 0.89 95% CI 0.75 to 1.06	⟷	Not significant
[21] RCT	178 people with diabetes mellitus with a healed foot ulcer	**Ulcer development , 12 months** 36/87 (41.4%) with foot-care education 35/85 (41.2%) with usual care	RR 0.97 95% CI 0.78 to 1.28	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Foot-care education involved a leaflet and a single individual 1-hour education session along with follow-up telephone call 1 month later Usual care involved the same foot-care leaflet but otherwise managed according to usual practice			

Amputation rates

Compared with usual care We don't know whether patient education is more effective at reducing the risk of amputation (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Amputation rates					
[16] RCT	352 people with diabetes attending 4 primary-care teams, randomised by primary-care team In review [15]	**Amputations , 12 months** with structured care with usual care Absolute results not reported Structured care involved a patient education session about foot care plus patient follow-up reminders plus prompts to healthcare providers to examine feet and provide education Usual care was not described	OR 0.32 95% CI 0.05 to 1.86	⟷	Not significant
[17] RCT	266 people with diabetes attending primary care In review [15]	**Ulcer and amputation rates (combined) , after 1.5 years** 10/127 (8%) with foot-care education 16/139 (12%) with usual care Foot-care education involved 9 sessions on foot care and skin hygiene, diabetes, risk factors, diet, and weight management Usual care was not defined	OR 0.66 95% CI 0.30 to 1.49	⟷	Not significant
[18] [19] RCT	530 people with diabetes without any obvious need for foot care In review [15]	**Amputation rates , after 7 years** 1/267 (0.4%) with education plus podiatric visits 0/263 (0%) with written foot-care instructions Education was delivered by a podiatrist and involved a 45-minute session covering footwear, hygiene, toenail cutting, emollient cream, avoiding risk, foot gymnastics, and preventive podiatric care plus podiatric visits of 30 to 60 minutes' duration for 1 year (as many times as judged appropriate by the podiatrist)	Reported as not significant P value not reported	⟷	Not significant
[20] RCT	227 people with diabetes, allocated according to social security number In review [15]	**Major amputation , after 2 years** 3% with foot-care education 10% with routine diabetes education	RR 0.28 95% CI 0.11 to 0.70 NNT 14 95% CI 8 to 15	●●○	foot-care education

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute numbers not reported Foot-care education involved a single 1-hour educational class about foot care			
[21] RCT	178 people with diabetes mellitus with a healed foot ulcer	**Amputation rates , 6 months** 3/87 (3%) with foot-care education 0/85 (0%) with usual care Foot-care education involved a leaflet and a single individual 1-hour education session along with follow-up telephone call 1 month later Usual care involved the same foot-care leaflet but otherwise managed according to usual practice	RR 0.96 95% CI 0.92 to 1.00	⟷	Not significant
[21] RCT	178 people with diabetes mellitus with a healed foot ulcer	**Amputation rates , 12 months** 9/87 (10%) with foot-care education 9/85 (11%) with usual care Foot-care education involved a leaflet and a single individual 1-hour education session along with follow-up telephone call 1 month later Usual care involved the same foot-care leaflet but otherwise managed according to usual practice	RR 1.00 95% CI 0.90 to 1.11	⟷	Not significant

Infection rates

No data from the following reference on this outcome. [15] [21]

Ulcer healing rate

No data from the following reference on this outcome. [15] [21]

Adverse effects

No data from the following reference on this outcome. [15] [21]

Further information on studies

Comment: The trials included in the systematic review had weak methods. [15] The flaws included the following: only one trial had blinded outcome assessment; one trial made no comment on loss to follow-up; some trials offered no comment on concealment of randomisation; the trials did not use an intention-to-treat approach; and the eligibility criteria with respect to risk of ulceration were described adequately in only one trial.

Clinical guide:
Given the devastating nature of serious lower extremity complications, including a component of foot-care education as part of general diabetes education would seem reasonable.

OPTION THERAPEUTIC FOOTWEAR

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- We don't know whether therapeutic footwear is effective in preventing foot ulcers or amputations in people with diabetes.

Benefits and harms

Therapeutic footwear versus usual footwear:

We found one systematic review (search date 1998), [13] which identified no RCTs, but found one non-RCT. [22] We also found one subsequent RCT. [23]

Ulcer development

Compared with usual footwear We don't know whether therapeutic footwear is more effective at reducing the incidence of foot ulcers after 1 to 2 years in people without severe foot deformity (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer development					
[22]	69 people with a previous diabetic foot ulcer In review [13] This was a non-randomised trial.	**Ulcer recurrence , 1 year** 27% with therapeutic shoes 58% with participants own ordinary shoes Absolute numbers not reported Therapeutic shoes were manufactured according to the Towey guidelines deep enough to fit customised insoles and toe deformities, and made with soft thermoformable leather along with semirocker soles	ARR 31% 95% CI 7% to 55% NNT 4 95% CI 2 to 14	●●●	therapeutic shoes
[23] RCT **3-armed trial**	400 people with diabetes mellitus and previous foot ulcer but without severe foot deformity, mean age 62 years	**Foot ulceration , 2 years** 15% with cork insert 14% with polyurethane insert 17% with usual footwear Absolute numbers not reported	RR 0.88 for cork insert *v* usual footwear 95% CI 0.51 to 1.52 RR 0.85 for polyurethane insert *v* usual footwear 95% CI 0.48 to 1.48	⟷	Not significant

Amputation rates

No data from the following reference on this outcome. [22] [23]

Infection rates

No data from the following reference on this outcome. [22] [23]

Ulcer healing rate

No data from the following reference on this outcome. [22] [23]

Adverse effects

No data from the following reference on this outcome. [22] [23]

Further information on studies

Comment: **Clinical guide:**
Individuals with significant foot deformities (such as hammer toes or a Charcot foot) should be considered for referral for assessment for customised shoes that can accommodate the altered foot anatomy. In the absence of significant deformities, high-quality well-fitting non-prescription footwear seems to be a reasonable option.

QUESTION What are the effects of treatments in people with diabetes with foot ulceration?

OPTION HUMAN SKIN EQUIVALENT

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- Human skin equivalent (applied weekly for a maximum of 5 weeks) seems better at promoting ulcer healing than saline-moistened gauze.

Benefits and harms

Human skin equivalent versus saline-moistened gauze:
We found one systematic review (search date 2006), [24] which identified one RCT. [25]

Ulcer healing rate

Compared with saline-moistened gauze Human skin equivalent is more effective at increasing ulcer healing rates after 12 weeks in people with chronic neuropathic non-infected foot ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[25] RCT	208 people aged 18 to 80 years with diabetes mellitus and chronic neuropathic non-infected foot ulceration In review [24]	**Rate of wound closure , 12 weeks** 63/112 (56%) with human skin equivalent 36/92 (38%) with saline-moistened gauze Human skin equivalent (Graftskin) applied weekly for a maximum of 5 weeks	OR 2.14 95% CI 1.23 to 3.74 P = 0.0042	●●○	human skin equivalent

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Saline-moistened gauze applied weekly, maximum time frame not reported			
[25] RCT	208 people aged 18 to 80 years with diabetes mellitus and chronic neuropathic non-infected foot ulceration In review [24]	**Recurrence of completely healed ulcers , 6 months** 3/51 (6%) with human skin equivalent 4/31 (13%) with saline-moistened gauze Human skin equivalent (Graftskin) applied weekly for a maximum of 5 weeks Saline-moistened gauze applied weekly, maximum time frame not reported	Reported as not significant P value not reported	⟷	Not significant

Amputation rates

Compared with saline-moistened gauze Human skin equivalent is more effective at reducing the risk of amputation after 12 weeks in people with chronic neuropathic non-infected foot ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Amputation rates					
[25] RCT	208 people aged 18 to 80 years with diabetes mellitus and chronic neuropathic non-infected foot ulceration In review [24]	**Amputation rates , 12 weeks** 7/112 (6%) with human skin equivalent 15/96 (16%) with saline-moistened gauze Human skin equivalent (Graftskin) applied weekly for a maximum of 5 weeks Saline-moistened gauze applied weekly, maximum time frame not reported	P = 0.028	○○○	human skin equivalent

Infection rates

Compared with saline-moistened gauze Human skin equivalent is more effective at reducing the risk of osteomyelitis after 12 weeks in people with chronic neuropathic non-infected foot ulcers (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Amputation rates					
[25] RCT	208 people aged 18 to 80 years with diabetes mellitus and chronic neuropathic non-infected foot ulceration In review [24]	**Osteomyelitis , 12 weeks** 3/112 (3%) with human skin equivalent 10/96 (10%) with saline-moistened gauze Human skin equivalent (Graftskin) applied weekly for a maximum of 5 weeks Saline-moistened gauze applied weekly, maximum time frame not reported	P = 0.04	○○○	human skin equivalent

Ulcer development

No data from the following reference on this outcome. [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] RCT	208 people aged 18 to 80 years with diabetes mellitus and chronic neuropathic non-infected foot ulceration In review [24]	**Adverse effects** with human skin equivalent with saline-moistened gauze The RCT found no serious adverse effects. Wound infections and cellulitis were equally frequent in both groups			

Further information on studies

Comment: **Clinical guide:**
Human skin equivalent may not be widely available.

OPTION PRESSURE OFF-LOADING (TOTAL-CONTACT OR NON-REMOVABLE CAST)

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- Pressure off-loading with total-contact casting or non-removable fibreglass casts successfully improves healing of ulcers.
- Removable-cast walkers rendered irremovable seem equally effective, but have the added benefit of requiring less technical expertise for fitting.

Benefits and harms

Pressure off-loading versus traditional dressing changes:

We found one systematic review (search date 1998), [26] which identified one RCT. [27]

Ulcer healing rate

Pressure off-loading with total-contact casting compared with traditional dressing changes Pressure off-loading with total-contact casting is more effective at increasing ulcer healing rates (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[27] RCT	40 people with diabetes and plantar foot ulcers but no signs of infection or gangrene In review [26]	**Ulcer healing** 19/21 (91%) with total-contact casting (in a mean of 42 days) 6/19 (32%) with traditional dressing (in a mean of 65 days) Casts were applied by an experienced physiotherapist, changed after 5 to 7 days, and then every	P <0.05	○○○	total-contact casting

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2 to 3 weeks until healing occurred People in the control group were provided with accommodative footwear and crutches or a walker, and were instructed to complete wet to dry dressing changes 2 to 3 times daily			

Infection rates

Pressure off-loading with total-contact casting compared with traditional dressing changes Pressure off-loading with total-contact casting is more effective at reducing infection rates (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infection rates					
[27] RCT	40 people with diabetes and plantar foot ulcers but no signs of infection or gangrene In review [26]	**Infection** 0/21 (0%) with total-contact casting 5/19 (26%) with traditional dressing	P <0.05	○○○	total-contact casting

Ulcer development

No data from the following reference on this outcome. [27]

Amputation rates

No data from the following reference on this outcome. [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[27] RCT	40 people with diabetes and plantar foot ulcers but no signs of infection or gangrene In review [26]	**Fungal infections** 3/21 (14%) with total-contact casting Not reported with traditional dressing	Significance assessment not reported		

Pressure off-loading versus removable cast/shoes:
We found 7 RCTs. [28] [29] [30] [31] [32] [33] [34]

Ulcer healing rate

Pressure off-loading with total-contact casting compared with removable casts/shoes Pressure off-loading with total-contact casting seems more effective at increasing ulcer healing after 12 weeks in people with non-infected neuropathic foot ulcers; however, we don't know if pressure off-loading with total-contact casts is more effective at increasing healing rates in the longer term (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[28] RCT **3-armed trial**	63 people with diabetes mellitus and non-infected neuropathic plantar foot ulcers The third arm evaluated half-shoe	**Ulcer healing , 30 days** 89% with total-contact casting 61% with removable-cast walker or half-shoe Absolute numbers not reported	P = 0.03	○○○	total-contact casting
[29] RCT	50 people with diabetes mellitus and non-infected neuropathic plantar foot ulcers	**Ulcer healing , 30 days** 13/24 (54%) with fibreglass casts 5/26 (19%) with specialised cloth shoes	P = 0.03	○○○	fibreglass casts
[30] RCT	50 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Ulcer healing , 12 weeks** 19/23 (83%) with irremovable cast 14/27 (52%) with removable-cast walker	P = 0.02	○○○	irremovable cast
[33] RCT	43 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Ulcer healing , 16 weeks** 6/23 (26%) with total-contact cast 6/20 (30%) with custom-made temporary footwear	Reported as not significant P value not reported	⟷	Not significant
[34] RCT	58 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Ulcer healing , 90 days** 24/29 (83%) with non-windowed fibreglass cast 23/29 (79%) with removable pneumatic cast	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [31] [32]

Amputation rates

Pressure off-loading with total-contact casting compared with removable shoes We don't know whether total-contact casts reduce the risk of amputation in people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Amputation rates					
[33] RCT	43 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Amputation rates** 1/20 (5%) with total-contact cast 0/23 (0%) with custom-made temporary footwear	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [28] [29] [30] [31] [32] [34]

Infection rates

Pressure off-loading with total-contact casting compared with removable pneumatic cast We don't know whether non-windowed total-contact fibreglass casts reduce the risk of infection in people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infection rates					
[34] RCT	58 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Infection rates** 5/29 (17%) with non-windowed fibreglass cast 6/29 (21%) with removable pneumatic cast	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [28] [29] [30] [31] [32] [33]

Ulcer development

No data from the following reference on this outcome. [28] [29] [30] [31] [32] [33] [34]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT	50 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Infection** 27% with non-removable-cast walker 42% with removable-cast walker Absolute results not reported	P = 0.4	⟷	Not significant
[30] RCT	50 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Skin maceration** 68% with non-removable-cast walker 38% with removable-cast walker Absolute results not reported	P = 0.04	○○○	removable-cast walker

No data from the following reference on this outcome. [28] [29] [31] [32] [33] [34]

Pressure off-loading versus non-removable cast/shoes:

We found two RCTs comparing pressure off-loading with a removable cast-walker made non removable. [31] [32]
Note: A removable-cast walker rendered non-removable is easier to apply.

Ulcer healing rate

Pressure off-loading using total-contact casting compared with pressure off-loading using a removable-cast walker made non-removable Pressure off-loading using a removable-cast walker rendered non-removable and pressure off-loading using total-contact casting seem equally effective at promoting ulcer healing (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[31] RCT	41 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Ulcer healing , 12 weeks** 74% with total-contact cast 80% with non-removable cast walker Absolute numbers not reported Standard total-contact cast versus a removable-cast walker rendered non-removable by wrapping it with a single layer of fibreglass casting material. All participants had weekly visits for wound care and debridements	P = 0.65	⟷	Not significant
[32] RCT	40 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Ulcer healing , 12 weeks** 95% with total-contact cast 85% with non-removable cast walker Absolute numbers not reported Fibreglass total-contact cast versus a removable-cast walker rendered non-removable by wrapping it with a plastic band. All participants had weekly visits for wound care and debridements	P = 0.21	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [31] [32]

Amputation rates

No data from the following reference on this outcome. [31] [32]

Infection rates

No data from the following reference on this outcome. [31] [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] RCT	40 people with diabetes mellitus and non-infected, non-ischaemic neuropathic plantar foot ulcers	**Infection** with total-contact cast with non-removable cast walker	The RCT found no significant differences in the number of people requiring antibiotics for local infections between fibreglass total-contact cast and a removable-	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported	cast walker rendered non-removable		

No data from the following reference on this outcome. [31]

Further information on studies

Comment: **Clinical guide:**
Soft-tissue infections and osteomyelitis are contraindications to total-contact casting. Pressure off-loading with the total-contact cast is the gold standard of care for chronic neuropathic non-infected, non-ischaemic plantar foot ulcers in individuals with diabetes mellitus. The trials of removable-cast walkers rendered irremovable suggest that this alternative approach may be preferable given that less technical expertise for fitting is required.

OPTION SYSTEMIC HYPERBARIC OXYGEN (FOR INFECTED ULCERS)

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- Systemic hyperbaric oxygen seems to be effective in treating people with severely infected ulcers, although it is unclear whether it is useful in people with non-infected, non-ischaemic ulcers.

Benefits and harms

Systemic hyperbaric oxygen versus usual care:

We found one systematic review (search date 2005), [35] which identified three systematic reviews evaluating hyperbaric oxygen therapy in the management of chronic diabetic foot ulcers. The first systematic review [36] included non-randomised trials and case series that did not meet our inclusion criteria and so is not discussed further. The second systematic review [37] identified 5 RCTs (175 people with diabetic ulcers), of which two RCTs were in people with infected diabetic ulcers. The third systematic review identified 4 RCTs, of which two RCTs of interest were also identified by the second systematic review. [38] The reviews did not pool results for the two RCTs of interest so these RCTs are reported separately below. [39] [40] We also found two subsequent RCTs. [41] [42]

Amputation rates

Compared with usual care Systemic hyperbaric oxygen may be more effective after 2 to 10 weeks at reducing the risk of major amputations in people with severely infected diabetic foot ulcers. However, we don't know whether systemic hyperbaric oxygen is more effective at reducing the risk of minor amputation at 2 to 10 weeks, but systemic hyperbaric oxygen may be more effective at reducing the risk of major and minor amputations at 52 to 92 weeks in people with severe chronic foot ulceration (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Amputation rates					
[39] RCT	70 people with severe infected diabetic foot ulcers with full-thickness gangrene or abscess, or a large infected ulcer that had not healed after 30 days	**Major amputation rates , 10 weeks** 3/35 (9%) with systemic hyperbaric oxygen (daily 90-minute sessions at 2.2–2.5 atmospheres) plus usual care 11/33 (33%) with usual care alone Usual care involved aggressive debridement, broad-spectrum in-	P = 0.016	○○○	systemic hyperbaric oxygen

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		travenous antibiotics, revascularisation if indicated, and optimised glycaemic control			
[40] RCT	30 people with chronic infected foot ulcers	**Major amputation** 2 with systemic hyperbaric oxygen (4 treatments with systemic hyperbaric oxygen; 45-minute sessions at 3 atmospheres) plus usual care 7 with usual care alone Usual care included debridement, intravenous antibiotics, and optimised glycaemic control	P <0.05	○○○	systemic hyperbaric oxygen
[40] RCT	30 people with chronic infected foot ulcers	**Minor amputation** 4 with systemic hyperbaric oxygen (daily 90-minute sessions at 2.2–2.5 atmospheres) plus usual care 2 with usual care alone Usual care included debridement, intravenous antibiotics, and optimised glycaemic control	Reported as not significant P value not reported	⟷	Not significant
[41] RCT	94 people with severe chronic foot ulceration, present for 3 months	**Major amputations , 12 months** 3/49 (6%) with systemic hyperbaric oxygen 1/45 (2%) with placebo People in the placebo arm received treatment with hyperbaric air Treatments were given for 85 minutes daily, 5 days a week, for 8 weeks	P value not reported		
[41] RCT	94 people with severe chronic foot ulceration, present for 3 months	**Minor amputations , 12 months** 4/49 (8%) with systemic hyperbaric oxygen 4/45 (9%) with placebo People in the placebo arm received treatment with hyperbaric air Treatments were given for 85 minutes daily, 5 days a week, for 8 weeks	P value not reported		
[42] RCT	100 people with severe chronic foot ulceration	**Major amputations , 92 weeks** 0/50 (0%) with systemic hyperbaric oxygen 19/50 (34%) with standard care Standard care: debridement, offloading, systemic antibiotic therapy, and supportive medical therapy	Reported as significant P value not reported	○○○	systemic hyperbaric oxygen
[42] RCT	100 people with severe chronic foot ulceration	**Minor amputations , 92 weeks** 4/50 (8%) with systemic hyperbaric oxygen 24/50 (48%) with standard care Standard care: debridement, offloading, systemic antibiotic thera-	Reported as significant P value not reported	○○○	systemic hyperbaric oxygen

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		py, and supportive medical therapy			

Ulcer healing rate

Compared with usual care Systemic hyperbaric oxygen seems more effective after 52 to 92 weeks at improving ulcer healing in people with severely infected diabetic foot ulcers (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[41] RCT	94 people with severe chronic foot ulceration, present for 3 months	**Ulcer healing , 12 months** 25/48 (52%) with systemic hyperbaric oxygen 12/42 (29%) with placebo People in the placebo arm received treatment with hyperbaric air Treatments were given for 85 minutes daily, 5 days a week, for 8 weeks	P = 0.03	○○○	systemic hyperbaric oxygen
[42] RCT	100 people with severe chronic foot ulceration	**Ulcer healing , 92 weeks** 33/50 (66%) with systemic hyperbaric oxygen 0/50 (0%) with standard care Standard care: debridement, offloading, systemic antibiotic therapy, and supportive medical therapy	P <0.05	○○○	systemic hyperbaric oxygen

No data from the following reference on this outcome. [39] [40]

Ulcer development

No data from the following reference on this outcome. [39] [40] [41] [42]

Infection rates

No data from the following reference on this outcome. [39] [40] [41] [42]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] RCT	70 people with severe infected diabetic foot ulcers with full-thickness	**Adverse effects** with systemic hyperbaric oxygen plus usual care			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	gangrene or abscess, or a large infected ulcer that had not healed after 30 days	with usual care alone Absolute results not reported The RCT reported that 2 people developed symptoms of barotraumata to the ear, but this did not interrupt treatment			
[41] RCT	94 people with severe chronic foot ulceration, present for 3 months	**Hypoglycaemia** 2/48 (4%) with systemic hyperbaric oxygen 4/42 (10%) with placebo	P value not reported		
[41] RCT	94 people with severe chronic foot ulceration, present for 3 months	**Myringotomy with tube placement** 2/48 (4%) with systemic hyperbaric oxygen 2/42 (5%) with placebo	P value not reported		
[41] RCT	94 people with severe chronic foot ulceration, present for 3 months	**Barotraumatic otitis** 1/48 (2%) with systemic hyperbaric oxygen 0/42 (0%) with placebo	P value not reported		

No data from the following reference on this outcome. [40] [42]

Further information on studies

Comment: **Clinical guide:**
Systemic hyperbaric oxygen therapy may be considered in an individual with severe infected diabetic foot ulcers with full-thickness gangrene or abscess, or with a large infected ulcer that has not healed in over 30 days. More widespread application of this technology cannot be recommended given the limited RCT data.

OPTION TOPICAL GROWTH FACTORS

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- Topical growth factors seem to increase healing rates, but there has been little long-term follow-up of people treated with these factors.

Benefits and harms

Platelet-derived growth factors versus placebo:

We identified one systematic review (search date 1998), [26] which identified three RCTs. [43] [44] [45] We also found three subsequent RCTs. [46] [47] [48]

Ulcer healing rate

Platelet-derived growth factors compared with placebo Platelet-derived growth factors are more effective at increasing ulcer healing rates. Autologous growth factors (platelet-rich plasma gel) are no more effective than saline gel at 12 weeks at increasing ulcer healing rates in people with diabetes mellitus and chronic full-thickness, non-ischaemic, non-infected foot ulceration (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[43] RCT	118 people In review [26]	**Non-healing rates** 32/61 (52%) with platelet-derived growth factor (30 micrograms/g once daily for up to 20 weeks) 43/57 (75%) with placebo	P = 0.01	○○○	platelet-derived growth factor
[44] RCT	382 people In review [26]	**Non healing** 62/123 (50%) with platelet-derived growth factor (100 micrograms/g, 30 micrograms/g) 83/127 (65%) with placebo	P = 0.007	○○○	platelet-derived growth factor
[45] RCT	81 people In review [26]	**Non-healing rates** 3/15 (20%) with CT-102 0.01% 15/21 (71%) with placebo	P = 0.01	○○○	platelet-derived growth factor
[46] RCT	113 people with diabetes mellitus and non-ischaemic foot ulceration	**Healing rates , 20 weeks** 47/55 (85%) with 0.01% recombinant human platelet-derived growth factor for up to 20 weeks 31/58 (53%) with placebo for up to 20 weeks	P <0.05	○○○	0.01% recombinant human platelet-derived growth factor
[47] RCT	146 people with diabetes mellitus and neuropathic non-infected, non-ischaemic plantar foot ulcers	**Complete ulcer healing , 20 weeks** 42% with becaplermin 100 micrograms/g (0.01%) plus Adaptic dressing 35% with Adaptic dressing alone Absolute numbers not reported All participants were instructed on daily dressing changes and optimal wound care and the importance of non-weight bearing, and were assessed on a weekly basis	P = 0.3	⟷	Not significant
[48] RCT	72 people with diabetes mellitus and chronic full-thickness, non-ischaemic, non-infected foot ulceration	**Ulcer healing rates , 12 weeks** 13/40 (33%) with platelet-rich plasma gel twice-weekly application for 12 weeks 9/32 (28%) with saline gel twice-weekly application for 12 weeks	P = 0.79	⟷	Not significant

Amputation rates

No data from the following reference on this outcome. [26] [46] [47] [48]

Infection rates

No data from the following reference on this outcome. [26] [46] [47] [48]

Ulcer development

No data from the following reference on this outcome. [26] [46] [47] [48]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[46] RCT	113 people with diabetes mellitus and non-ischaemic foot ulceration	**Adverse effects** 13% with growth factor 17% with placebo Absolute numbers not reported Nature of adverse effects not clear	Reported as not significant P value not reported	⟷	Not significant
[48] RCT	72 people with diabetes mellitus and chronic full-thickness, non-ischaemic, non-infected foot ulceration	**Adverse effects , 12 weeks** 60 with platelet-rich plasma gel 62 with saline gel Only 2 adverse effects (contact dermatitis and maceration) were related to treatment	Significance assessment not reported		

No data from the following reference on this outcome. [26] [47]

Topical growth factors versus usual care:

We found one RCT. [49]

Ulcer healing rate

Compared with usual care We don't know whether becaplermin is more effective at promoting ulcer healing in people with diabetes mellitus and chronic full-thickness, non-ischaemic, non-infected foot ulceration (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[49] RCT	250 people with diabetes mellitus and chronic full-thickness, non-ischaemic, non-infected foot ulceration	**Ulcer healing** 36% with becaplermin 100 micrograms/g (0.01%) 32% with good ulcer care Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [49]

Amputation rates

No data from the following reference on this outcome. [49]

Infection rates

No data from the following reference on this outcome. [49]

Adverse effects

No data from the following reference on this outcome. [49]

Protein-based growth factors versus placebo:

We found one systematic review (search date 1998), [26] which identified one RCT. [50] We also found two subsequent RCTs. [51] [52]

Ulcer healing rate

Protein-based growth factors compared with placebo/control Arginine–glycine–aspartic acid matrix, and insulin may be more effective at increasing ulcer healing rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[50] RCT	65 people In review [26]	**Non-healing rates , 10 weeks** 26/40 (65%) with matrix 23/25 (92%) with placebo Although the arginine–glycine–aspartic acid matrix is not strictly a growth factor, the matrix is designed to facilitate the rapid and organised re-population of the site by fibroblasts, endothelial cells, and keratinocytes	P = 0.02	○○○	arginine–glycine–aspartic acid matrix
[51] RCT	24 people with diabetes mellitus and severe foot complications including infected ulceration, abscess, or toe gangrene	**Time to complete healing** 19.6 days with daily wound dressing with a saline-soaked gauze impregnated with 5 to 10 units of insulin 53.5 days with povidone 0.05% All participants initially received appropriate debridement, abscess drainage, and amputation of any gangrenous digits, along with antibiotics	P <0.001	○○○	insulin
[52] RCT **3-armed trial**	46 people with diabetes mellitus and non-ischaemic, non-infected foot ulcers	**Complete ulcer healing rates , 12 weeks** 3/15 (20%) with lactoferrin (an iron-binding glycoprotein) 2.5% gel	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		3/15 (20%) with lactoferrin 8.5% gel 3/16 (19%) with placebo gel			

Amputation rates

No data from the following reference on this outcome. [26] [51] [52]

Infection rates

No data from the following reference on this outcome. [26] [51] [52]

Ulcer development

No data from the following reference on this outcome. [26] [51] [52]

Adverse effects

No data from the following reference on this outcome. [26] [51] [52]

Epidermal growth factors versus placebo:

We found two RCTs. [53] [54]

Ulcer healing rate

Epidermal growth factors compared with placebo/control We don't know whether epidermal growth factors are more effective at 4 to 12 weeks at increasing ulcer healing rates in people with diabetes mellitus and non-ischaemic foot ulceration (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[53] RCT **3-armed trial**	61 people with diabetes mellitus and non-ischaemic foot ulceration	**Complete wound healing rates, 12 weeks** 20/21 (95%) with 0.04% human epidermal growth factor plus control cream 12/21 (57%) with 0.02% human epidermal growth factor plus control cream 8/19 (42%) with control cream alone All interventions applied daily Control cream contained a protein-free calf blood extract	P = 0.0003 for 0.04% human epidermal growth factor *v* other two treatments combined	○○○	0.04% human epidermal growth factor

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[54] RCT	50 people with diabetes mellitus and non-ischaemic foot ulceration	**Complete ulcer healing rate , 4 weeks** 7/30 (23%) with epidermal growth factor 2/20 (10%) with placebo	P = 0.3	⟷	Not significant

Amputation rates

No data from the following reference on this outcome. [53] [54]

Infection rates

No data from the following reference on this outcome. [53] [54]

Ulcer development

No data from the following reference on this outcome. [53] [54]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[54] RCT	50 people with diabetes mellitus and non-ischaemic foot ulceration	**Adverse effects** with epidermal growth factor with placebo The RCT reported no topical or generalised adverse effects			

No data from the following reference on this outcome. [53]

Retinoids versus placebo:
We found one RCT. [55]

Ulcer healing rate

Retinoids compared with saline Tretinoin seems more effective at 16 weeks at increasing ulcer healing rates in people with diabetes mellitus and non-ischaemic, non-infected foot ulceration (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[55] RCT	24 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration	**Complete ulcer healing , 16 weeks** 6/13 (46%) with 0.05% tretinoin 2/11 (18%) with placebo (saline solution)	P = 0.03	◌◌◌	0.05% tretinoin

Amputation rates

No data from the following reference on this outcome. [55]

Infection rates

No data from the following reference on this outcome. [55]

Ulcer development

No data from the following reference on this outcome. [55]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[55] RCT	24 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration	**Adverse effects** with 0.05% tretinoin with placebo (saline solution) The RCT found that 1 person with 0.05% tretinoin and 1 person with saline solution reported mild to moderate pain (no data analysis reported)			

Basic fibroblast growth factor versus placebo:

We found one RCT. [56]

Ulcer healing rate

Basic fibroblast growth factor compared with placebo We don't know whether basic fibroblast growth factor is more effective at promoting healing in people with diabetes mellitus and non-ischaemic, non-infected foot ulceration (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[56] RCT **3-armed trial**	150 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration measuring 900 mm^2 or less Other arm included: 0.001% basic fibroblast growth factor	**Ulcer healing , 8 weeks** 30/45 (67%) with 0.01% basic fibroblast growth factor 22/47 (47%) with placebo	P = 0.12	⟷	Not significant
[56] RCT **3-armed trial**	150 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration measuring 900 mm^2 or less Other arm included: 0.01% basic fibroblast growth factor	**Ulcer healing , 8 weeks** 27/47 (57%) with 0.001% basic fibroblast growth factor 22/47 (47%) with placebo	P = 0.65	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [56]

Amputation rates

No data from the following reference on this outcome. [56]

Infection rates

No data from the following reference on this outcome. [56]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[56] RCT **3-armed trial**	150 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration measuring 900 mm^2 or less	**Adverse effects** 3/49 (6.1%) with 0.01% basic fibroblast growth factor 1/48 (2.1%) with 0.001% basic fibroblast growth factor 3/51 (5.9%) with placebo Adverse effects included wound infection, increase in alkaline	P value not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		phosphatase and LDH, pain at the administration site			

Bilayered cellular matrix versus usual care:

We found one RCT. [57]

Ulcer healing rate

Bilayered cellular matrix compared with usual care We don't know whether bilayered cellular matrix is more effective at promoting complete ulcer healing in people with diabetes mellitus and non-ischaemic, non-infected foot ulceration at 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[57] RCT	40 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration	**Complete ulcer healing , 12 weeks** 7/20 (35%) with bilayered cellular matrix 4/20 (20%) with usual care	P value not reported		

Infection rates

Bilayered cellular matrix compared with usual care We don't know whether bilayered cellular matrix is more effective at reducing infections in people with diabetes mellitus and non-ischaemic, non-infected foot ulceration at 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infection rates					
[57] RCT	40 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration	**Ulcer-related infection rates , 12 weeks** 2/20 (10%) with bilayered cellular matrix 0/20 (0%) with usual care	P value not reported		

Ulcer development

No data from the following reference on this outcome. [57]

Amputation rates

No data from the following reference on this outcome. [57]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[57] RCT	40 people with diabetes mellitus and non-ischaemic, non-infected foot ulceration	**Adverse effects** 2/20 (10%) with bilayered cellular matrix 0/20 (0%) with usual care	P value not reported		

Further information on studies

Comment: **Clinical guide:**
No randomised trials have compared optimal pressure off-loading with topical growth factor application in terms of ulcer healing rates.

OPTION DEBRIDEMENT OR WOUND DRESSINGS

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- We don't know whether debridement or wound dressings are effective in healing ulcers.
- However, debridement with hydrogel and dimethyl sulfoxide wound dressings does seem to help ulcer healing.
- Debridement and wound dressings have been included together because the exact mechanism of the treatment can be unclear (e.g., hydrogel).

Benefits and harms

Debridement with hydrogel versus other debridement techniques or standard wound care:
We found one systematic review (search date 2009, 6 RCTs, 492 people). [58]

Ulcer healing rate

Debridement with hydrogel compared with standard care or hydrogel Debridement with hydrogel may be more effective at increasing ulcer healing rates after 12 weeks compared with standard care; however, we don't know whether hydrogel purilon is more effective at increasing ulcer healing compared with hydrogel intrasite (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[58] Systematic review	198 people 3 RCTs in this analysis	**Ulcer healing , 12 weeks** with hydrogel with gauze dressing or standard wound care Absolute results not reported	RR 1.84 95% CI 1.30 to 2.61 ARI 23% 95% CI 10% to 26% NNT 5 95% CI 2 to 10	●○○	hydrogel
[58] Systematic review	74 people with diabetes mellitus and foot ulceration Data from 1 RCT	**Ulcer healing , 10 weeks** 35% with hydrogel purilon 19% with hydrogel intrasite Absolute numbers not reported The systematic review evaluated the study from abstract form only	P value not reported		

Ulcer development

No data from the following reference on this outcome. [58]

Amputation rates

No data from the following reference on this outcome. [58]

Infection rates

No data from the following reference on this outcome. [58]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[58] Systematic review	Number of people in the analysis unclear	**Adverse effects** 22 events with hydrogel 36 events with good wound care	RR 0.60 95% CI 0.38 to 0.95	●○○	hydrogel

Surgical debridement versus other debridement techniques or standard wound care:
We found one systematic review (search date 2009, 6 RCTs, 492 people). [58]

Ulcer healing rate

Surgical debridement compared with usual care Surgical debridement may be no more effective at promoting ulcer healing (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[58] Systematic review	140 people Data from 1 RCT	**Ulcer healing** 21/22 (95%) with surgical debridement 19/24 (79%) with conservative care Conventional management involved pressure relief and regular dressings; the type of dressing was not reported Surgical excision involved debridement or removal of bone segments underlying the lesion, and surgical closure	RR 1.21 95% CI 0.96 to 1.51 P = 0.1	⟷	Not significant

Infection rates

Surgical debridement compared with conservative treatment We don't know whether surgical debridement is more effective at reducing infection (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infection rates					
[58] Systematic review	46 people Data from 1 RCT	**Infection** 1/22 (5%) with surgical debridement 3/24 (13%) with conservative treatment Conventional management involved pressure relief and regular dressings; the type of dressing was not reported Surgical excision involved debridement or removal of bone segments underlying the lesion, and surgical closure	RR 0.33 95% CI 0.03 to 3.47	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [58]

Amputation rates

No data from the following reference on this outcome. [58]

Adverse effects

No data from the following reference on this outcome. [58]

Debridement with larvae versus other debridement techniques or standard wound care:

We found one systematic review (search date 2009, 6 RCTs, 492 people). [58]

Ulcer healing rate

Debridement with larvae compared with debridement with hydrogel We don't know whether debridement with larvae is more effective at promoting ulcer healing (very-low quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[58] Systematic review	140 people Data from 1 RCT	**Ulcer healing , 12 weeks** 5/70 (7%) with larvae 2/70 (3%) with hydrogel	RR 2.5 95% CI 0.5 to 12.4 Published in abstract form only; duration of follow-up unclear	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [58]

Infection rates

No data from the following reference on this outcome. [58]

Amputation rates

No data from the following reference on this outcome. [58]

Adverse effects

No data from the following reference on this outcome. [58]

Wound dressings versus each other:

We found two systematic reviews [59] [60] and one subsequent RCT. [61] The first systematic review (search date 2006) found no RCTs on silver-based dressings for foot ulcers in people with diabetes. [59] The second systematic review (search date 1998, 9 RCTs, number of people unclear) did not perform a meta-analysis, but reported by specific wound dressing comparisons. [60] We have reported the comparisons here where the RCTs found fitted our inclusion criteria of >20 people per study.

Ulcer healing rate

Wound dressings compared with each other We don't know which wound dressing is more effective at 4 to 12 weeks at promoting ulcer healing (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[59] Systematic review	40 people 2 RCTs in this analysis	**Complete healing rates** with hydrocellular dressing with alginate-based dressings Absolute results not reported	OR 2.44 95% CI 0.78 to 7.57	⟷	Not significant
[59] Systematic review	40 people with neuropathic foot ulceration Data from 1 RCT	**Time to healing , 4 weeks** with adhesive "hydroactive" polyurethane gel dressing with hydrocellular dressing Absolute results not reported	WMD +4.76 days 95% CI –7.41 days to +16.93 days	⟷	Not significant
[59] Systematic review	40 people with neuropathic foot ulceration Data from 1 RCT	**Reduction in wound size , 4 weeks** with adhesive "hydroactive" polyurethane gel dressing with hydrocellular dressing	WMD –1.1 mm^2 95% CI –41.7 mm^2 to +39.5 mm^2	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Absolute results not reported			
[59] Systematic review	75 people with non-ischaemic, non-infected diabetic foot ulcers Data from 1 RCT	**Complete healing** with collagen–alginate dressing with saline-moistened gauze Absolute results not reported	OR 1.07 95% CI 0.35 to 3.25	⟷	Not significant
[59] Systematic review	75 people with non-ischaemic, non-infected diabetic foot ulcers Data from 1 RCT	**Mean time to complete healing** with collagen–alginate dressing with saline-moistened gauze Absolute results not reported	WMD +2.80 days 95% CI –8.8 days to +14.4 days	⟷	Not significant
[59] Systematic review	40 people with diabetic foot ulceration Data from 1 RCT	**Ulcer healing , 15 weeks** with dimethyl sulfoxide with conventional treatment Absolute results not reported Conventional treatment not described	OR 11.44 95% CI 3.28 to 39.92	●●●	dimethyl sulfoxide
[59] Systematic review	35 people with diabetes and "cavity" ulcers of the foot Data from 1 RCT	**Ulcer healing rates , 12 weeks** with cadexomer iodine ointment with standard dressings Absolute results not reported Standard dressing not described	OR 3.04 95% CI 0.59 to 15.56	⟷	Not significant
[61] RCT	39 people	**Healing rate , 4 weeks** with moist dressing (calcium alginate) with dry dressing (fine mesh gauze) Absolute results not reported	OR 1.2 95% CI 0.3 to 4.9 P = 0.8	⟷	Not significant

No data from the following reference on this outcome. [60]

Ulcer development

No data from the following reference on this outcome. [59] [60] [61]

Amputation rates

No data from the following reference on this outcome. [59] [60] [61]

Infection rates

No data from the following reference on this outcome. [59] [60] [61]

Adverse effects

No data from the following reference on this outcome. [59] [60] [61]

Wound dressings versus conventional treatment:

We found two systematic reviews. [59] [60] The first systematic review (search date 2006) found no RCTs on silver-based dressings for foot ulcers in people with diabetes. [59] The second systematic review (search date 1998, 9 RCTs, number of people unclear) did not perform a meta-analysis, but reported by specific wound dressing comparisons. [60] We have reported the comparisons here where the RCTs found fitted our inclusion criteria of >20 people per study.

Ulcer healing rate

Dimethyl sulfoxide dressing compared with conventional treatment Dimethyl sulfoxide seems more effective at 15 weeks at increasing ulcer healing rates (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[59] Systematic review	40 people with diabetic foot ulceration Data from 1 RCT	**Ulcer healing , 15 weeks** with dimethyl sulfoxide with conventional treatment Absolute results not reported Conventional treatment not described	OR 11.44 95% CI 3.28 to 39.92	●●●	dimethyl sulfoxide

No data from the following reference on this outcome. [60]

Ulcer development

No data from the following reference on this outcome. [59] [60]

Amputation rates

No data from the following reference on this outcome. [59] [60]

Infection rates

No data from the following reference on this outcome. [59] [60]

Adverse effects

No data from the following reference on this outcome. [59] [60]

Wound dressings versus standard dressings:

We found two systematic reviews. [59] [60] The first systematic review (search date 2005) found no RCTs on silver-based dressings for foot ulcers in people with diabetes. [59] The second systematic review (search date 1998, 9 RCTs, number of people unclear) did not perform a meta-analysis, but reported by specific wound dressing comparisons. [60] We have reported the comparisons here where the RCTs found fitted our inclusion criteria of >20 people per study.

Ulcer healing rate

Cadexomer iodine ointment compared with standard dressings We don't know whether cadexomer iodine ointment is more effective at 12 weeks at increasing ulcer healing rates in people with diabetes and cavity ulcers of the foot (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[60] Systematic review	35 people with diabetes and "cavity" ulcers of the foot Data from 1 RCT	**Ulcer healing rates , 12 weeks** with cadexomer iodine ointment with standard dressings Absolute results not reported Standard dressing not described	OR 3.04 95% CI 0.59 to 15.56	⟷	Not significant

No data from the following reference on this outcome. [60]

Ulcer development

No data from the following reference on this outcome. [59] [60]

Amputation rates

No data from the following reference on this outcome. [59] [60]

Infection rates

No data from the following reference on this outcome. [59] [60]

Adverse effects

No data from the following reference on this outcome. [59] [60]

Further information on studies

Comment: In the systematic review on debridement, the trials were generally small and of poor methodological quality.

Clinical guide:
We have included debridement and wound dressings together in the same option as the exact mechanism of the treatment can be unclear (e.g., hydrogel). Hydrogel functions by increasing the moisture of the wound environment and this effect may be more significant than its effect on debridement.

OPTION PRESSURE OFF-LOADING (WITH FELTED FOAM OR PRESSURE-RELIEF HALF-SHOE)

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- We don't know whether pressure off-loading with felted foam or pressure-relief half-shoe is effective in treating diabetic foot ulcers.

Benefits and harms

Pressure off-loading with felted foam versus pressure-relief half-shoe:

We found one RCT. [62]

Ulcer healing rate

Pressure off-loading with felted foam dressings compared with pressure-relief half-shoe Pressure off-loading with felted foam dressings and pressure-relief half-shoe seem equally effective at 10 weeks at promoting ulcer healing (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[62] RCT	61 people with diabetes mellitus and a neuropathic plantar forefoot ulcer	**Time to ulcer healing , 10 weeks** 79.6 days with felted foam 83.2 days with a half-shoe	P = 0.61	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [62]

Amputation rates

No data from the following reference on this outcome. [62]

Infection rates

No data from the following reference on this outcome. [62]

Adverse effects

No data from the following reference on this outcome. [62]

Felted foam padding directly applied to the skin versus being inserted into footwear:

We found one RCT. [63]

Ulcer healing rate

Felted foam padding applied to the skin compared with being inserted into footwear Felted foam padding applied to the skin and padding inserted into footwear seem equally effective at promoting ulcer healing (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[63] RCT	32 people with diabetes mellitus and a grade 1 or 2 neuropathic plantar forefoot ulcer	**Number of people with wound closure , 4 weeks** 73% with pressure off-loading felted foam dressings directly applied to the skin 74% with pressure off-loading felted foam dressings inserted into footwear Absolute numbers not reported	P = 0.9	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [63]

Amputation rates

No data from the following reference on this outcome. [63]

Infection rates

No data from the following reference on this outcome. [63]

Adverse effects

No data from the following reference on this outcome. [63]

Pressure relief half-shoe versus non-removable casts:

See pressure off-loading versus removable casts/shoes, p 11 .

Further information on studies

Comment: See clinical guide under pressure off-loading (non-removable cast), p 11 .

OPTION SYSTEMIC HYPERBARIC OXYGEN (FOR NON-INFECTED, NON-ISCHAEMIC ULCERS)

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- Systemic hyperbaric oxygen seems to be effective in treating people with severely infected ulcers, although it is unclear whether it is useful in people with non-infected, non-ischaemic ulcers.

Benefits and harms

Systemic hyperbaric oxygen plus usual care versus usual care alone:

We found one systematic review, [35] which identified three systematic reviews. The first systematic review [36] included non-randomised trials and case series that did not meet our inclusion criteria and so is not discussed further. The second systematic review [37] identified 5 RCTs (175 people with diabetic ulcers), of which one RCT included people with non-infected diabetic ulcers, which we report here. [64] The third systematic review did not identify any RCTs in people with non-infected, non-ischaemic ulcers.

Ulcer healing rate

Hyperbaric oxygen plus usual care compared with usual care alone Hyperbaric oxygen plus usual care may be no more effective at promoting ulcer healing at 4 weeks in people with non-infected neuropathic foot ulcers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing					
[64] RCT	28 people with neuropathic foot ulcers In review [37]	**Complete healing , 4 weeks** 2/14 (14%) with systemic hyperbaric oxygen therapy (90-minute sessions at 2.5 atmospheres twice daily for 2 weeks) 0/13 (0%) with usual care Usual care was not defined	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	28 people with neuropathic foot ulcers In review [37]	**Reduction in ulcer surface area , 4 weeks** 62% with systemic hyperbaric oxygen therapy (90 minute sessions at 2.5 atmospheres twice daily for 2 weeks) 22% with usual care Absolute numbers not reported Usual care was not defined	Reported as not significant P value not reported	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [64]

Amputation rates

No data from the following reference on this outcome. [64]

Infection rates

No data from the following reference on this outcome. [64]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[64] RCT	28 people with neuropathic foot ulcers In review [37]	**Adverse effects** with systemic hyperbaric oxygen therapy with usual care The RCT reported 1 case of mild barotrauma to the ear			

Further information on studies

Comment: None.

OPTION HUMAN CULTURED DERMIS

- For GRADE evaluation of interventions for Diabetes: foot ulcers and amputations, see table, p 42 .
- Human cultured dermis does not seem effective at promoting healing.

Benefits and harms

Human cultured dermis versus usual care:

We found one systematic review (search date 1998, 2 RCTs). [26]

Ulcer healing rate

Compared with usual care Human cultured dermis substitute plus usual care is no more effective at 12 weeks at increasing ulcer healing rates (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer healing rate					
[26] Systematic review	331 people attending hospital outpatient clinics with diabetic foot ulcers with no signs of infection or severe vascular compromise	**Ulcer healing , 12 weeks** with topical human cultured dermis (weekly for 8 weeks) plus usual care with usual care alone Absolute results not reported	+21% increase in ulcer healing with human cultured dermis 95% CI –13% to +36%	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		All participants received wound debridement and were encouraged to avoid weight bearing on the affected limb			

Infection rates

Compared with usual care Human cultured dermis substitute plus usual care seems no more effective at 12 weeks at reducing ulcer infection rates (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Infection rates					
[26] Systematic review	Population details unclear Data from 1 RCT	**Ulcer infections , 12 weeks** with topical human cultured dermis substitute plus usual care (weekly for 8 weeks) with usual care Absolute results not reported All participants received wound debridement and were encouraged to avoid weight bearing on the affected limb	Reported as not significant P value not reported	⟷	Not significant

Ulcer development

No data from the following reference on this outcome. [26]

Amputation rates

No data from the following reference on this outcome. [26]

Adverse effects

No data from the following reference on this outcome. [26]

Further information on studies

Comment: **Clinical guide:**
Human cultured dermis may not be widely available.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Human skin equivalent Consists of two allogenic layers containing human skin cells. One layer is formed by dermal cells (human fibroblasts) and the second layer is formed by epidermal cells. Human skin equivalent produces cytokines and growth factors involved in the skin healing process.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Major amputations Amputations that are above or below the knee.

Minor amputations Amputations that involve partial removal of a foot, including toe or forefoot resections.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Pressure off-loading The use of different techniques designed to minimise the amount of force applied to the ulcer site.

Systemic hyperbaric oxygen Exposing a person to a high oxygen, high-pressure environment designed to improve oxygen delivery to the ulcer site.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Debridement or wound dressings One systematic review updated, new evidence added. [58] Categorisation unchanged (Unknown effectiveness) as there remains insufficient good-quality evidence to assess the effects of debridement or wound dressing on diabetic foot ulcers.

Education New evidence added. [21] Categorisation unchanged (Unknown effectiveness) as there remains insufficient good-quality evidence to assess the effects of education on diabetic foot ulcers and amputations.

Pressure off-loading (total-contact or non-removable cast) New evidence added. [33] [34] Categorisation unchanged (Likely to be beneficial).

Systemic hyperbaric oxygen (infected ulcers) New evidence added. [41] [42] Categorisation unchanged (Likely to be beneficial).

Topical growth factors New evidence added. [49] [56] [57] Categorisation unchanged (Likely to be beneficial).

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Disclaimer

GRADE **Evaluation of interventions for Diabetes: foot ulcers and amputations.**

Important outcomes	Amputation rates, Infection rates, Ulcer development, Ulcer healing rate								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions to prevent foot ulcers and amputations in people with diabetes?									
1 (2002) [13]	Ulcer development	Screening and referral to foot-care clinics versus usual care	4	0	0	0	0	High	
1 (1001) [13]	Amputation rates	Screening and referral to foot-care clinics versus usual care	4	0	0	0	0	High	
5 (1553) [16] [17] [18] [19] [20] [21]	Ulcer development	Education versus usual care	4	–3	–1	–1	0	Very low	Quality points deducted for flaws with randomisation, blinding, follow-up, and statistical analysis. Consistency point deducted for conflicting results. Directness point deducted for composite outcomes
5 (1553) [16] [17] [18] [19] [20] [21]	Amputation rates	Education versus usual care	4	–3	–1	–1	0	Very low	Quality points deducted for flaws with randomisation, blinding, follow-up, and statistical analysis. Consistency point deducted for conflicting results. Directness point deducted for composite outcomes
2 (469) [22] [23]	Ulcer development	Therapeutic footwear versus usual footwear	4	–1	–1	0	0	Low	Quality point deducted for randomisation flaws. Consistency point deducted for conflicting results
What are the effects of treatments in people with diabetes with foot ulceration?									
1 (208) [25]	Ulcer healing rate	Human skin equivalent versus saline-moistened gauze	4	0	0	0	0	High	
1 (208) [25]	Amputation rates	Human skin equivalent versus saline-moistened gauze	4	0	0	0	0	High	
1 (208) [25]	Infection rates	Human skin equivalent versus saline-moistened gauze	4	0	0	0	0	High	
1 (40) [27]	Ulcer healing rate	Pressure off-loading versus traditional dressing changes	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for RR >2
1 (40) [27]	Infection rates	Pressure off-loading versus traditional dressing changes	4	–1	0	0	+1	High	Quality point deducted for sparse data. Effect-size point added for RR >2
5 (264) [28] [29] [30] [33] [34]	Ulcer healing rate	Pressure off-loading versus removable cast/shoes	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (43) [33]	Amputation rates	Pressure off-loading versus removable cast/shoes	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (58) [34]	Infection rates	Pressure off-loading versus removable cast/shoes	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (81) [31] [32]	Ulcer healing rate	Pressure off-loading versus non-removable cast/shoes	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes	Amputation rates, Infection rates, Ulcer development, Ulcer healing rate								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
4 (294) [39] [40] [41] [42]	Amputation rates	Systemic hyperbaric oxygen versus usual care	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
2 (194) [41] [42]	Ulcer healing rate	Systemic hyperbaric oxygen versus usual care	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
6 (867) [26] [46] [47] [48]	Ulcer healing rate	Platelet-derived growth factors versus placebo	4	0	0	0	0	High	
1 (250) [49]	Ulcer healing rate	Topical growth factors versus usual care	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of data
3 (135) [50] [51] [52]	Ulcer healing rate	Protein-based growth factors versus placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for lack of consistency in benefits with different types of topical growth factors
2 (111) [53] [54]	Ulcer healing rate	Epidermal growth factors versus placebo	4	–1	–1	0	0	Low	Quality point deducted for sparse data. Consistency point deducted for conflicting results
1 (24) [55]	Ulcer healing rate	Retinoids versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (150) [56]	Ulcer healing rate	Basic fibroblast growth factor versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [57]	Ulcer healing rate	Bilayered cellular matrix versus usual care	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (40) [57]	Infection rates	Bilayered cellular matrix versus usual care	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
4 (272) [58]	Ulcer healing rate	Debridement with hydrogel versus other debridement techniques or standard wound care	4	–3	0	0	0	Very low	Quality points deducted for methodological flaws, incomplete reporting of results, and reporting from abstract
1 (46) [58]	Ulcer healing rate	Surgical debridement versus other debridement techniques or standard wound care	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about comparator (type of dressing)
46 (1) [58]	Infection rates	Surgical debridement versus other debridement techniques or standard wound care	4	–2	0	0	0	Low	Quality points deducted for sparse data and wide confidence intervals suggesting the result should be interpreted with caution
1 (140) [58]	Ulcer healing rate	Debridement with larvae versus other debridement techniques or standard wound care	4	–3	0	0	0	Very low	Quality points deducted for sparse data and methodological flaws
6 (229) [59] [61]	Ulcer healing rate	Wound dressings versus each other	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws. Directness point deducted for large number of interventions compared
1 (40) [59]	Ulcer healing rate	Wound dressings versus conventional treatment	4	–2	0	–1	+2	Moderate	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about comparator. Effect-size points added for OR >5

Important outcomes	Amputation rates, Infection rates, Ulcer development, Ulcer healing rate								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (35) [59]	Ulcer healing rate	Wound dressings versus standard dressings	4	–2	0	–1	+1	Low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about comparator. Effect-size point added for OR >2
1 (61) [62]	Ulcer healing rate	Pressure off-loading with felted foam versus pressure-relief half-shoe	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (32) [63]	Ulcer healing rate	Felted foam padding directly applied to the skin versus being inserted into footwear	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (28) [64]	Ulcer healing rate	Systemic hyperbaric oxygen plus usual care versus usual care alone	4	–2	0	0	0	Low	Quality point deducted for sparse data and incomplete reporting of results
2 (331) [26]	Ulcer healing rate	Human cultured dermis versus usual care	4	0	0	0	0	High	
1 (unclear) [26]	Infection rates	Human cultured dermis versus usual care	4	–1	0	0	0	Moderate	Quality point deducted for unclear number of people included in the RCT.

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.